APPENDIX A

NEBILET TABLETS 5 mg

Logo

SCHEDULING STATUS:
S3

PROPRIETARY NAME
(and dosage form):

NEBILET TABLETS 5 mg

COMPOSITION
Nebilet Tablets 5 mg contains nebivolol hydrochloride equivalent to 5 mg **nebivolol**

PHARMACOLOGICAL CLASSIFICATION
A 7.1.3 - Other hypotensives

PHARMACOLOGICAL ACTION
Pharmacodynamics:
Nebivolol is a racemate of two enantiomers, SRRR-nebivolol (or d-nebivolol) and RSSS-nebivolol (or l-nebivolol). It combines two pharmacological activities: -

- It is a competitive & selective B1-receptor antagonist which is attributable to the d-enantiomer
- It has mild vasodilating properties, possible due to an interaction with the L-arginine/nitric oxide pathway

Nebivolol reduces heart rate & blood pressure at rest & during exercise. In healthy volunteers it has no significant effect on maximal exercise or endurance.
An in-vitro and in-vivo experiment in animals showed that nebivolol has no intrinsic sympathicomimetic activity and at pharmacological doses has no membrane stabilising effect. It is also devoid of alpha-adrenergic antagonism at therapeutic doses.
Pharmacokinetics
Nebivolol can be given with or without meals with peak plasma concentrations occuring within 2 - 6 hours after dosing. It is extensively metabolised partly to active hydroxy metabolites. The bioavailability of nebivolol averages 12% in extensive metabolisers (EM's) & is virtually complete in poor metabolisers (PM's), but the mean bioavailability of the separate enantiomers and hydroxylated metabolites was fairly similar between EM's & PM's and no differences were found in the pharmacodynamic effects.
Steady-state plasma levels for nebivolol are reached within 24 hours in most subjects (EM's). The elimination half-lives of the hydroxy-metabolites of both enantiomers average 24 hours in EM's and are twice as long in PM's. Plasma concentrations are dose proportional and the pharmacokinetics of nebivolol are unaffected by age. Nebivolol is highly protein bound; d-nebivolol being 98.1% and l-nebivolol 97,9% bound to albumin. About 52% of the dose is excreted in urine and about 15% in the faeces in PM's one week after administration.

INDICATIONS:
Treatment of mild to moderate essential hypertension.

CONTRA-INDICATIONS
Hypersensitivity to Nebilet
Liver insufficiency or liver function impairment.
Pregnancy and lactation
Nebilet is contra-indicated in:

- Cardiogenic shock
- Uncontrolled heart failure
- Sick sinus syndrome, including sino-atrial block
- 2nd & 3rd degree heart block
- Untreated phaeochromocytoma
- Metabolic acidosis
- Bradycardia (heart rate < 50 bpm)
- Bronchial asthma
- Hypotension

- History of bronchospasm & bronchial asthma
- Severe peripheral circulatory disorders
- Verapamil therapy
- Children, as safety and efficacy has not been demonstrated

WARNINGS
Beta-adrenergic antagonists may increase the sensitivity to allergens and the severity of anaphylactic reactions

DOSAGE AND DIRECTIONS FOR USE:
Adults
Take one 5 mg tablet daily, preferable at the same time of the day, with or without meals
Combination with other antihypertensive agents:
An additional antihypertensive effect has been observed only when Nebilet 5 mg is combined with hydrochlorthiazide 12.5 - 25 mg
Patients with renal insufficiency:
The recommended starting dose is 2.5 mg daily. The daily dose may be increased to 5 mg if needed.
Patients with hepatic insufficiency:
There is no data in patients with hepatic insufficiency or impaired liver function. Therefore the use of Nebilet is contra-indicated in these patients.
Elderly:
In patients over 65 years, the recommended starting dose is 2.5 mg daily. The dose may be increased to 5 mg daily if needed. Due to limited experience in patients above 75 years, caution must be exercised and these patients monitored closely.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:
Side-Effects:
The most common side-effects (incidence between-1 - 10%) are headache, dizziness, tiredness & paraesthesia. Other side-effects reported in 1% of patients are: diarrhoea, constipation, nausea, dyspnoea & oedema. Typical beta-adrenergic antagonist side-effects reported in less than 1% of patients are: bradycardia, slowed AV conduction/AV-block, hypotension, heart failure, increase of intermittent claudication, impaired vision, impotence, depression, nightmare, dyspepsia, flatulence, vomiting, bronchospasm and rash.
The following side-effects have also been reported with some beta-adrenergic antagonists: hallucinations, psychoses, confusion, cold/cyanotic extremities, Raynaud phenomenon, dry eyes and mucocutaneous toxicity of the practolol-type, sleep disturbances and abdominal cramping.
Congestive heart failure or heart block may be precipitated in patients with underlying cardiac disorders. Pneumonitis, pleurisy, paraesthesia, peripheral neuropathy, overt psychosis, myopathies, skin rash, pruritis, and reversible alopecia have been reported. Ocular symptoms include decreased tear production, blurred vision and soreness.
Haematological reactions include nonthrombocytopenic purpura, thrombocytopenia, and less frequently agranulocytosis. Transient eosinophilia can occur.
Metabolic changes affect glucose control and cholesterol concentrations. Other side effects include a lupus like syndrome, male impotence, hypoglycaemia, sclerosing peritonitis and retroperitoneal fibrosis. Severe peripheral vascular disease and even peripheral gangrene may be precipitated.
Special Precautions:
Cardiovascular:
Beta-adrenergic antagonists should not be used in patients with untreated congestive heart failure, unless their condition has been stabilized. One of the pharmacological actions of beta-blockers is to reduce the heart rate.
Abrupt discontinuation of therapy may cause exacerbation of angina pectoris in patients suffering from ischaemic heart disease. Discontinuation of therapy should be gradual (over a period of 1-2 weeks) and patients should be advised to limit the extent of their physical activity during the period that their medicine may be discontinued. If the pulse rate drops below 50-55 bpm at rest and/or the patient experiences symptoms suggestive of bradychardia, the dosage should be reduced. Beta-adrenergic antagonists should be used with caution in:

- Peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication) as the disorders may be aggravated
- 1st degree heart block because of the negative effect of beta-blockers on conduction time
- Prinzmetal's angina due to unopposed alpha receptor mediated coronary artery vasoconstriction

Beta-blockers may increase the number and duration of anginal attacks
Metabolic/Endocrinological:
Symptoms of hypoglycaemia (tachycardia, palpitations) may be masked in diabetic patients. Tachycardic symptoms may be masked in hyperthyroidism. Abrupt withdrawal may intensify symptoms.
Respiratory:
Bronchospasm may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases.
Other:

Psoriasis may be aggravated. Patients with phaeochromocytoma should not receive beta-blockers without concomitant alpha-adrenoreceptor blocking therapy.
Beta-blockers may unmask myasthenia gravis.
Adverse reactions are more common in patients with renal decompensation, and in patients who receive beta-blockers intravenously.

INTERACTIONS
Calcium Antagonists:
Caution should be exercised when administering beta-blockers with calcium antagonists of the verapamil or diltiazem type because of their negative effect on contractility and atrio-ventricular conduction. Exaggeration of these effects can occur particularly in patients with impaired ventricular function and/or SA or AV conduction abnormalities. Neither medicine should therefore be administered intravenously within 48 hours of discontinuing the other.
Anti-arrhythmics:
Caution should be exercised when administering beta-blockers with Class I anti-arrhythmic drugs and amiodarone as their effect on atrial conduction time and their negative inotropic effect may be potentiated. Such interactions can have life threatening consequences.
Clonidine:
Beta-blockers increase the risk of rebound hypertension after sudden withdrawal of chronic clonidine treatment.
Digitalis:
Digitalis glycosides associated with beta-blockers may increase atrio-ventricular conduction times. Nebivolol does not influence the kinetics of digoxin & clinical trials have not shown any evidence of an interaction.
Special note: Digitalisation of patients receiving long term beta-blocker therapy may be necessary if congestive cardiac failure is likely to develop. The combination can be considered despite the potentiation of the negative chronotropic effect of the two medicines. Careful control of dosages and of individual patient's response (notably pulse rate) is essential in this situation.
Insulin & Oral Antidiabetic drugs:
Glucose levels are unaffected, however symptoms of hypoglycaemia may be masked.
Anaesthetics:
Concomitant use of beta-blockers & anaesthetics e.g. ether, cyclopropane & trichloroethylene may attenuate reflex tachycardia & increase the risk of hypotension
Other:
Provided Nebilet is taken with a meal & an antacid between meals, the two treatments can be co-prescribed.
Sympathicomimetic agents may counteract the effect of beta-blockers.
Concomitant administration of tricyclic antidepressants, barbiturates & phenothiazines may increase the blood pressure lowering effect.
Concomitant administration of serotonin re-uptake inhibitors or other compounds predominantly metabolised by the CYPZD6 pathway may delay oxidative metabolism of beta-blockers

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
Symptoms:
Bradycardia, hypotension, bronchospasm and acute cardiac insufficiency
Treatment:
Blood glucose levels should be checked and symptomatic and supportive therapy given.

IDENTIFICATION:
An off-white, circular, biconvex half-scored tablet

PRESENTATION:
Tablets are blister packed in PVC/Aluminium blister in pack sizes of 28's or 30's.

STORAGE INSTRUCTIONS:
Store below 25°C.
KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER:
34/7.1.3/0495

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DATE OF PUBLICATION OF THIS PACKAGE INSERT:
01/11/2000

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New addition to this site: May 2004
Source: Pharmaceutical Industry

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